REMARKS/ARGUMENTS

1. Amendments

New independent claim 77 now recites an isolated fusion molecule comprising a human IgG heavy chain constant region sequence capable of binding to a human IgG inhibitory receptor directly functionally connected to a human IgE heavy chain constant region sequence capable of binding to a human IgE receptor wherein said fusion molecule is capable of attenuating a human IgE receptor mediated response. The recitations of claims 78 and 82 have been added to Claim 77. Applicants have clarified that the fusion molecule is capable of binding both the IgG inhibitory receptor and the IgE receptor.

Applicants have amended the claim dependencies of Claims 79 - 81 as requested by the Examiner at the Interview on December 16, 2003.

Applicants have incorporated the recitations of Claim 77 into Claim 89 to make Claim 89 independent.

Applicants have added Claim 96 which recites an isolated fusion molecule comprising a human IgG heavy chain constant region sequence capable of binding to a human IgG inhibitory receptor directly functionally connected to a human IgE heavy chain constant region sequence capable of binding to a human IgE receptor wherein said fusion molecule is capable of binding to the IgG inhibitory receptor and to the IgE receptor and wherein said IgG heavy chain constant region sequence consists of the hinge-CH2-CH3 portion of an IgG heavy chain constant region. Support for this claim can be found in original Claim 77 and in Claim 87.

No new matter is being added by these amendments

Claims 77, 79-81 and 83- 96 are now pending in the application.

2. Interview

Application No.: 09/847,208
Filed: May 1, 2001
Docket No.: 39754-0672A

Applicants would like to thank Examiner Huynh and Examiner Chan for the courtesies extended to them during the Interview on December 16, 2003. At the interview, Applicants explained why they felt that the claimed invention, as amended, was not anticipated by Presta et al or rendered obvious by the various combinations of references cited by the Examiner in the Office Action. These arguments are set forth below under the various headings. Applicants also explained why the claimed invention, as amended, is fully enabled by the specification and that there is sufficient written description of the claimed invention in the specification.

The Examiner indicated that she would reconsider the Presta reference based on the discussion.

3. Information Disclosure Statement

Applicants filed an Information Disclosure Statement with 49 cited references on August 14, 2003. The Examiner is requested to review and make these references of record by initialing and returning the PTO-1449 form.

Applicants enclose herewith a Second Supplemental Information Disclosure Statement citing references which are discussed in this response. The Examiner is requested to review and make these references of record by initialing and returning the PTO-1449 form.

4. Rejection under 35 U.S.C. 112, first paragraph- Enablement

Claims 77 - 95 stand rejected under 35 U.S.C. 112, first paragraph because the specification allegedly is not enabling for certain claims.

Applicants note with appreciation that the Examiner has indicated that an isolated fusion molecule comprising SEQ ID NO:7 is enabled. Accordingly, Applicants request that the Examiner remove her rejection of Claim 93 which recites a fusion molecule of SEQ ID NO:7 and claims 94-95 which depend from Claim 93.

The Examiner has indicated that an isolated fusion molecule comprising an IgG heavy chain constant region capable of binding to an IgG inhibitory receptor functionally connected to

an IgE heavy chain constant region sequence capable of binding to an IgE receptor wherein the IgE heavy chain constant region consists of the CH2-CH3-CH4 of a native human IgE heavy chain constant region (illustration number 10 in the Office Action). Applicants have amended Claim 89 to put it into independent form. Claim 90 depends from Claim 89. Withdrawal of this rejection for claims 89 and 90 is now respectfully requested.

The Office Action indicates that the specification allegedly does not provide enablement for any fusion molecule comprising any IgG heavy chain constant region sequence capable of binding to any IgG inhibitory receptor functionally connected to any IgE heavy chain constant region sequence capable of binding to any IgE receptor as set forth in claims 77-95. There is allegedly insufficient guidance as to the structure of any other fusion molecule. Further the term "comprising" is open-ended and allegedly expands the fusion molecule to include additional amino acids at either or both ends. Further there is allegedly no working example demonstrating that any fusion molecule is effective for preventing allergy.

Applicants respectfully disagree for the following reasons.

First Applicants note that they have amended Claim 77 to recite that the IgG heavy chain constant region, the IgG receptor, the IgE heavy chain constant region and the IgE receptor are human and that the IgG heavy chain constant region and the IgE heavy chain constant region are directly connected.

The nature of the invention

The present invention is from the field of recombinant DNA technology and immunology. In particular, the invention concerns certain novel fusion molecules that are capable of cross-linking a native human IgG inhibitory receptor with a native human IgE receptor, and find utility in the management of IgE-mediated allergic diseases and other disorders mediated by IgE receptors. While the therapeutic strategy underlying the present invention is both novel and unobvious, the fusion molecules themselves have a relatively simple structure, and can be made and tested by standard techniques that were well known in the art at the time of making the present invention. Furthermore, at the time the present invention was made, there

Application No.: 09/847,208
Filed: May 1, 2001
Docket No.: 39754-0672A

was a lot of information known in the art about the. interaction of IgG inhibitory receptors and IgE receptors with antibody constant regions, which provides valuable information for the construction of the fusion molecules of the present invention.

The level of ordinary skill in the art

It is well established that the level of skill in the art of recombinant DNA technology is relatively high, and is typically represented by the knowledge of a Ph.D. scientist with several years of experience in the pertinent field.

Fusion Molecules Comprising First and Second Polypeptide Sequences are Enabled

The present application describes, by way of example, additional non-essential but advantageous amino acid sequences and other elements that find use with the first and second polypeptides of the fusion molecules of the invention. For example, the first and second polypeptide sequences of the fusion molecule can be joined using various linkers (described in the Specification at page 27, lines 4-15). Also, the fusion molecules may contain posttranslational modifications, either naturally occurring or artificial, for example, acetylation, glycosylation and prenylation (see Specification page 12, line 24, through page 13, line 13). The Specification teaches that fusion polypeptide variants can be constructed that contain advantageous insertions of various amino acid sequences (page 14, lines 11-14), resulting in fusion molecules that have improved affinity for their respective IgG or IgE Fc receptors (Specification, page 21, lines 9-28). The fusion molecules of the invention can also comprise multiple copies of the IgG and IgE Fc domains, for example, IgG-IgG-IgE or IgG-IgE-IgG Fc configurations find use with the invention, as described in page 25, lines 6-17. Fusion polypeptides further comprising signal sequences for intracellular localization or extracellular export (page 42, lines 17-19), and peptide sequence tags to facilitate fusion molecule purification (page 42, lines 29-3 1) also find use with the fusion molecules of the invention.

As outlined above, the Specification provides sufficient guidance to make a variety of advantageous fusion molecules comprising first and second polypeptide sequences. Applicants submit that fusion molecules comprising first and second polypeptides are fully enabled in view

of 1) guidance provided throughout the Specification[1] (as described above), 2) the routine nature of recombinant DNA engineering and the production of chimeric or variant polypeptides, as known in the art, and 3) the high level of technical competence of one of ordinary skill in the immunology, genetics and protein-chemistry arts. The routine nature of manipulation of DNA and protein molecules is well known, as evidenced by the publications cited in the Specification *(see,* especially, page 12, line 20 through page 13, line 13, page 28, lines 19-27, page 41, lines 1--25, and page 43, line 24 through page 44, line 21). Detailed protocols for the construction of the fusion molecule variants described in the Specification is not necessary for one of ordinary skill to practice the claimed invention without undue experimentation.

The Examiner asserts that use of the term "comprising" in the claims results in an infinite number of possible nucleotide sequences, and it is not possible to predict which of those molecules will have desired functional activity. Applicants disagree. Applicants point out that Claim 77 and all claims dependent on Claim 77 contain the functional limitation that the IgG and IgE Fc domains (either native or variants) have the ability to bind to their respective cell surface receptors. The Specification teaches which amino acids are necessary for receptor binding (see page 21, lines 9-28) as well as methods to determine the affinity of an Fc domain for its cognate receptor (see, for example, page 26, lines 15-25). Thus, use of the term "comprising" does not result in an infinite number of fusion molecules with unpredictable activities, and the identification of constructs that meet the limitation of the claims does not require undue experimentation.

Applicants submit that use of the open-ended transitional phrase "comprising" in Claim 77 is appropriate, and that claim as well as all claims dependent on that claim are enabled and commensurate in scope with the disclosure, and are allowable. The Examiner is respectfully requested to withdraw this rejection.

The Office Action indicates that there is no *in vivo* working example demonstrating that any fusion molecule mentioned above is effective in preventing any allergy. Applicants submit

---

[1] Applicants point out that the guidance provided in the Specification is found both in the Experimental Example as well as in the description of other preferred embodiments elsewhere in the Specification.

that pages 53 and 54 using the passive cutaneous anaphylaxis model provides sufficient example.

The Office Action indicates that it is known that the relationship between the amino acid sequence of a protein and its tertiary structure are not well understood and are not predictable. since the term "is" in Claim 88 is open-ended, it expands the hinge-CH2-CH3 portion of the IgG heavy chain constant region to include additional amino acids to be added. There is allegedly insufficient guidance as to which undisclosed amino acids are to be added and whether the resulting fusion chain would bind. Applicants have claimed only those fusion molecules which bind. Applicants have provided in the specification, sufficient examples of how one skilled in the art could test to determine whether the resulting fusion molecule would bind. It is not improper to require some experimentation on the part of the skilled artisan. Applicants request withdrawal of this rejection.

5. Rejection under 35 U.S.C. 112, first paragraph - Written Description

In the Office Action, the Examiner rejects Claims 77-95 for allegedly lacking written description (35 U.S.C. § 112, first paragraph). Specifically, the Examiner alleges that there is insufficient written description in the Specification for the same fusion molecules that were rejected on the basis of lack of enablement (see above, and Office Action, pages 6-9).

To satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention (e.g., *Vas-Cath, Inc. v. Mahurkar,* 935 F.2d at 563, 19 USPQ 2d at 1116 and *Gentry Gallery, Inc. v. Berkline Corp.,* 134 F.3d 1473, 45 USPQ 2d 1498 [Fed. Cir. 1998]). Applicants assert that they have met this requirement. Applicants emphasize that sufficient written description must be ascertained in view of one skilled in the art. "It is not required that the application describe the claim limitations in greater detail than the invention warrants. The description must be sufficiently clear that persons of skill in the art will recognize that the applicant made the invention having those limitations" *(Martin v. Mayer,* 823 F.2d 500, 3 USPQ 2d 1333 [Fed. Cir. 1987]),

Multiple Fusion Molecules are Described in the Specification

The Examiner alleges that the Specification discloses insufficient written description of the structure of fusion molecules of the invention (with the exception of the fusion molecule recited in Claim 93, *i.e.,* SEQ ID NO: 7) to support a claim to a larger genus of fusion molecules.

Applicants must respectfully disagree. The specification teaches that the CH2-CH3 interface of the IgG Fc domain contains the binding sites for the FcγRIIb IgG inhibitory receptor. (page 21, lines 13 - 15). The Specification further teaches that six amino acid residues of the human IgE heavy chain CH3 domain are involved in binding to the high affinity IgE receptor FcεRI. Furthermore, as described above, the Specification describes multiple fusion molecules in addition to the fusion molecule of SEQ ID NO: 7. For example, the Specification describes fusion molecules where the first and second polypeptide sequences of the fusion molecule are connected by use of linkers (see Specification page 27, lines 4-15). Also, the fusion molecules may contain post translational modifications, either naturally occurring or artificial, for example, acetylation, glycosylation or prenylation (as described in the Specification at page 12, line 24, through page 13, line 13). The Specification describes advantageous fusion molecule variants (page 14, lines 11-14), where the variants have improved affinity for their respective IgG or IgE receptors (Specification, page 21, lines 9-28). The Specification describes fusion molecules comprising multiple copies of IgG and IgE Fc domains, for example, IgG-IgG-IgE or IgG-IgE-IgG Fc configurations (page 25, lines 6-17). Fusion polypeptides further comprising signal sequences for intracellular localization or extracellular export (page 42, lines 17-19), and peptide sequence tags to facilitate fusion molecule purification the fusion molecules (page 42, lines 29-31) are also described.

In view of the fusion molecules described above and the level of skill in the art, applicants assert that sufficient representative fusion molecules are adequately described in the Specification (without undue detail) to support a genus of fusion molecules, as recited in Claim 77, and all claims dependent on Claim 77. Applicants respectfully request the withdrawal of this rejection.

6. Rejection under 35 U.S.C. 102(b) as being anticipated by Presta et al.

Claims 77-78, 82-86 and 91-92 stand rejected under 35 U.S.C. 102(b) as being anticipated by Presta *et al.* (J. Biol. Chem 269(42): 26368-26373 (1994). Presta *et al.* teach various isolated fusion molecules such as IgGEL and IgG2/E3.

In order to be anticipatory the reference must disclose each element of the claimed invention. Lewmar Marine Inc. v. Varient Inc., 3 USPQ2d 1766 (Fed. Cir. 1987).

Presta *et a*l. teaches the specific residues of the epsilon chain of IgE involved in binding to the FcϵRI alpha chain. Presta does this by replacing a portion of the heavy chain IgG residues in an IgG molecule with IgE residues. In IgG2/E3 Presta took a vector with anti-p185 IgG1 sequences and replaced the Fcγ2 portion of IgG1 (amino acid residues Cys 239-Gly 361) with IgE amino acid residues Cys 357 to Gly 497. This inserts the binding region of the heavy chain region of IgE into the IgG1 antibody. In other words, Presta *et al.* is merely performing a domain swap. In the vector IgGEL, Presta *et al.* describes a vector where certain IgG residues were replaced with specific IgE residues, (*i.e.* IgG aa residues 291-305 replaced with IgE loop CD aa residues 407-420; IgG aa residues 329-337 replaced with IgE loop EF, aa residues 445-453; IgG aa residues 349-352 replaced with IgE loop FG aa residues 465-469 and finally IgG aa residues 239-249 replaced with IgE hinge aa residues 357-365). Again this is simply a domain swap of portions of the heavy chain region of IgG with portions of the heavy chain region of IgE. Presta *et al.* at page 26373 first column states that the Cγ2 domain in IgG is used for binding to the high affinity receptor FcγRI. Applicants enclose herewith another paper by the Presta lab (Shields et al., J. Biol. Chem. Vol. 276, no. 9, 6591-6604 (2001)) which identifies the residues required in the Fc portion of IgG for binding to the FcγRII receptor.

Presta does not disclose a fusion molecule capable of binding both the human IgE receptor and a human IgG inhibitory receptor. In Presta et al., the IgE Fc portion is inserted in place of the IgG Fc portion. Applicants believe that the single antibody molecule of Presta *et al.* would not be able to bind the IgG receptor because the amino acid residues required for binding have been removed. Secondly, the antibody molecule of Presta *et al.* would not be able to bind both the IgG receptor and the IgE receptor because of steric hindrance since the IgE heavy chain constant region was inserted into the IgG heavy chain constant region.

Because all of the limitations of claim 77, as amended, are not found in Presta *et al.*, this reference cannot be anticipatory and accordingly, withdrawal of this rejection is respectfully requested.

7. Rejection under 35 U.S.C. 103(a) as being unpatentable over Presta *et al.* in view of WO88/09344

Claims 77 and 79-81 stand rejected as allegedly being obvious over Presta *et al.* in view of WO88/09344 publication. Presta *et al.* has been discussed. The Office action indicates that WO88/09344 teaches various polypeptide linkers such as Gly-Gly-Gly-Gly-Ser which is at least 15 amino acid residues in length.

This rejection is traversed for the following reasons:

As discussed above Presta *et al.* does not teach or suggest a fusion molecule comprising a human IgG heavy chain constant region capable of binding to a human IgG inhibitory receptor directly functionally connected to a human IgE heavy chain constant region sequence capable of binding to a human IgE receptor. WO88/09344 does not correct this deficiency. WO88/09344 merely teaches different types of linkers. In the absence of a teaching of a human IgG heavy chain constant region capable of binding to a human IgG inhibitory receptor directly functionally connected to a human IgE heavy chain constant region sequence capable of binding to a human IgE receptor claims 77 and 78-81 are not obvious. Withdrawal of this rejection is respectfully requested.

8. Rejection under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 5,336,603 in view of WO95/14779, Basu *et al.* and Daeron *et al.*

Claims 77-78, 82-89 and 91-92 stand rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 5,336,603 in view of WO95/14779, Basu *et al.*, and Daeron *et al.* It allegedly would have been obvious to one of ordinary skill in the art to substitute the CD4 molecule as taught by the '603 patent for the human IgE heavy chain constant region sequence that is capable of binding to an IgE receptor as taught by WO95/14779 or Basu *et al.* for a fusion

molecule comprising the IgG heavy chain constant region that is capable of binding to IgG inhibitory receptor fused to an IgE heavy chain constant region sequence that is capable of binding to an IgE receptor. One having ordinary skill in the art at the time would allegedly have been motivated to do so because Daeron *et al.* teach that IgE induced mediator release is inhibited by cross-linking FcεRI to FcγRIIbI

This rejection is traversed for the following reasons.

U.S. Patent No. 5,336,603 teaches soluble secreted adhesons comprising the CD4 protein. The CD4 adheson ordinarily binds to the recognition sites of HIV and the purpose of the patent is to design candidates for therapeutically sequestering these HIV sites, thereby blocking viral infectivity. The '603 patent teaches fusing the CD4 polypeptide with a protein with a long plasma life such as an immunoglobulin constant domain. The purpose of this fusion is to increase the half-life of the CD4 polypeptide. The '603 patent teaches the CD4 peptide linked to the IgG1 heavy chain constant region. There is no teaching or suggestion in the '603 patent to replace the CD4 molecule in the immunoadheson with an IgE heavy chain constant region. Such a replacement would be against the purpose of the '603 patent.

WO95/14779 teaches mutated human IgE fragments comprising the second, third and fourth constant region domains of the IgE heavy chain. The publication teaches mutated glycosylated polypeptides which include at least a part of the IgE heavy chain sufficient to bind to the FcεRI or FcεRII receptor sites on human cells which are useful in the investigation and amelioration of allergic conditions. WO95/14779 does not teach or suggest directly linking the IgE heavy chain constant region with an IgG heavy chain constant region in one molecule.

Basu *et al.*, teach that the Fc region of IgE comprising epsilon 2, epsilon 3 and epsilon 4 domains are sufficient for binding to the IgE high affinity receptor. Basu does not teach or suggest directly linking the Fc region of IgE with the Fc region of IgG.

Daeron *et al.* teach that linking the FcεRI receptor with the FcγRII low affinity receptor will result in inhibition of IgE induced release of mediator and cytokines. Daeron *et al.* accomplishes this linkage by establishing an artificial system, using a rat basophilic leukemia cell transfected with mouse FcγRII and naturally expressing rat FcεRI receptor. The cells were then exposed to three different antibodies to link the mouse FcγRII with the rat FcεRI receptor. These antibodies were rat anti-mouse FcγRII/III Fab'2; mouse anti-rat Ig Fab'2 and rat IgE. There is no

teaching or suggestion in Daeron *et al.* to make a single molecule directly linking the Fc regions of IgE with the Fc regions of IgG.

Applicants believe that the claimed invention is not obvious in light of the combination of the cited references for the following reasons.

Where claimed subject matter has been rejected as obvious in view of a combination of prior art references, a proper analysis under 103 requires, inter alia, consideration or two factors: (1) whether the prior art would have suggested to those of ordinary skill in the art that they should make the claimed composition or device, or carry out the claimed process and (2) whether the prior art would also have revealed that in so making or carrying out, those of ordinary skill would have a reasonable expectation of success. In re Vaeck 947 F 2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

First, there is no teaching or suggestion in the combination of the references to fuse the heavy constant region of the IgE molecule with the heavy chain constant region of the IgG molecule. While the '603 patent teaches immunoadhesons of CD4 fused with IgG, the purpose of adding IgG was to improve the half-life of the CD4. Both WO95/14779 and Basu teach the region of the heavy chain of IgE which binds to the IgE receptor. Neither teaches or suggests fusing the heavy chain region of IgE with the heavy chain region of IgG. Finally Daeron, while suggesting linking the FcεRI receptor with the FcγRII receptor, does not teach a single chain molecule which would accomplish this.

Secondly, there is no motivation in the cited references to combine the teachings of the references to arrive at the claimed invention. The '603 patent uses the IgG heavy chain region to confer prolonged half-life to the CD4 peptide. It provides no motivation to replace the CD4 peptide with an IgE heavy chain region. Daeron et al. discusses the advantages of linking the FcεRI receptor with the FcγRII receptor. However, Daeron proposes a solution to this using multiple antibody molecules. There is no motivation in Daeron to fuse the heavy chain of IgE with the heavy chain of IgG. Furthermore, while Daeron uses the constant region of a complete rat IgE antibody to bind to the FcεRI receptor, Daeron uses the variable region of rat anti-mouse FcγRII/III Fab'2 to bind to the mouse FcγRII receptor. Accordingly, Daeron does not provide motivation to generate a fusion molecule comprising the heavy chain constant region of IgE fused to the heavy chain constant region of IgG. If anything, Daeron *et al.*, teaches away from

the claimed invention by teaching that linking of the FcεRI receptor to the FcγRII receptor can be achieved through the use of multiple antibodies.

Finally, none of the references, either alone or in combination provide a reasonable expectation of success from the claimed invention.

Absent a suggestion in the art to make the claimed invention, a motivation in the cited references to combine the references into the claimed invention and a reasonable expectation of success, the claimed invention is not obvious. Withdrawal of this rejection is respectfully requested.

9. Rejection under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 5,336,603 in view of WO95/14779, Basu *et al.* and Daeron *et al.* and further in view of WO88/09344

Claims 79-81 stand rejected as allegedly being obvious over U.S. Patent No. 5,336,603 in view of WO95/14779, Basu *et al.* and Daeron *et al.* and further in view of WO88/09344. U.S. Patent No. 5,336,603, WO95/14779, Basu *et al.*, and Daeron *et al.* have been discussed. The Office action indicates that WO88/09344 teaches various polypeptide linkers such as Gly-Gly-Gly-Gly-Ser which is at least 15 amino acid residues in length.

This rejection is traversed for the following reasons:

As discussed above the combination of U.S. Patent No. 5,336,603, WO95/14779, Basu et al., and Daeron *et al.* does not teach or suggest a fusion molecule comprising a human IgG heavy chain constant region capable of binding to a human IgG inhibitory receptor directly functionally connected to a human IgE heavy chain constant region sequence capable of binding to a human IgE receptor. WO88/09344 does not correct this deficiency. WO88/09344 merely teaches different types of linkers. In the absence of a teaching of a human IgG heavy chain constant region capable of binding to a human IgG inhibitory receptor directly functionally connected to a human IgE heavy chain constant region sequence capable of binding to a human IgE receptor claims 79-81 are not obvious. Withdrawal of this rejection is respectfully requested.

10. Rejection under 35 U.S.C. 103 as being unpatentable over U.S. Patent No. 5,336,603 in view of WO95/14779, Basu *et al.* and Daeron *et al.* and further in view of U.S. Patent No. 5,925,351

Claim 85 stands rejected as allegedly being obvious over U.S. Patent No. 5,336,603 in view of WO95/14779, Basu *et al.* and Daeron *et al.* and further in view of U.S. Patent No. 5,925,351. U.S. Patent No. 5,336,603, WO95/14779, Basu *et al.*, and Daeron *et al.* have been discussed. The Office action indicates that U.S Patent No. 5,925,351 teaches a fusion molecule LT-β-F-Fc comprising a first polypeptide of LT-β-F-R functionally connected to the human Fc domains of various IgG such as IgG1, IgG2, IgG3, and IgG4 based on the desirable secondary effector functions. Therefore, it allegedly would have been obvious to one of ordinary skill in the art to substitute the Fc domains of IgG1 as taught by the '603 patent with the Fc domains of various IgG such as IgG2, IgG3 or IgG4.

This rejection is traversed for the following reasons:

As discussed above the combination of U.S. Patent No. 5,336,603, WO95/14779, Basu *et al.*, and Daeron *et al.* does not teach or suggest a fusion molecule comprising a human IgG heavy chain constant region capable of binding to a human IgG inhibitory receptor directly functionally connected to a human IgE heavy chain constant region sequence capable of binding to a human IgE receptor. U.S. Patent No. 5,925,351 does not correct this deficiency. In the absence of a teaching of a human IgG heavy chain constant region capable of binding to a human IgG inhibitory receptor directly functionally connected to a human IgE heavy chain constant region sequence capable of binding to a human IgE receptor claim 85 is not obvious. Withdrawal of this rejection is respectfully requested.

11. Secondary Considerations

Applicants believe that the patent office has not established a *prima facie* case of obviousness for the reasons set forth above.

However, Applicants enclose herewith three references which indicate that others in the field have recognized that there is a long felt need for this invention and that the invention has been greeted with enthusiasm.

Applicants enclose two papers they and others in their laboratory have published in prestigious, peer-reviewed journals on the invention:

Zhu et la., "A novel human immunoglobulin Fcγ-Fcε bifunctional fusion protein inhibits FcεRI mediated degranulation", Nature Medicine Vol. 8, 518-521 (2002)

Kepley et al., "FcεRI-FcγRII Coaggregation inhibits IL-16 production from human langerhans-like dendritic cells" Clinical Immunology Vol.108 89-94 (2003)

Applicants also enclose a news article published by NIAID News entitled "Experimental Therapy Stops Allergic Reactions in Mice".

Applicants believe that this application is in condition for allowance.

Should the Examiner find that there are any further issues outstanding, a personal interview before issuance of a further Office Action is hereby requested. The Examiner is invited to call the undersigned attorney to arrange the time for a personal interview.

Please direct any calls in connection with this application to the undersigned at the number provided below.

Respectfully submitted,

Date: December 29, 2003

Leslie A. Mooi
Reg. No. 37,047

HELLER EHRMAN WHITE & McAULIFFE LLP
Customer No. 25213
275 Middlefield Road
Menlo Park, California 94025
Telephone: (650) 324-7000
Facsimile: (650) 324-0638

SV 471811 v1
12/29/03 9:33 AM (39754.0672)